REMARKS

Claims 73, 74, 85-94, 99-110, 180, 181, 186, 187 and 189-191 were pending in this application. Applicants have canceled claim 187, without prejudice to Applicants' rights to pursue the subject matter of the canceled claim in a related application. In order to expedite the prosecution of the present application and without conceding to the validity of the Examiner's rejections, Applicants have amended claims 73, 74, 89, 91, 180, 181 and 186 to more particularly point out and distinctly claim the subject matter that Applicants regard as their invention. In particular, claim 73 has been amended to recite a sustained release formulation comprising palivizumab. Claim 74 has been amended to recite a pharmaceutical composition adapted for pulmonary delivery comprising palivizumab. Claims 89 and 91 have been amended to correct the misspelling of the word "intravenously". Claims 180 and 181 have been amended to recite a method of preventing a RSV infection, or treating or ameliorating one or more symptoms associated with a RSV infection in a human subject comprising administering to the lungs of the human subject a prophylactically or therapeutically effective amount of a composition comprising palivizumab. In view of the amendments to claims 180 and 181, claim 186 has been amended to recite that palivizumab is administered by a nebulizer or inhaler.

Applicants have also added new claims 231-263 to more particularly point out and distinctly claim the subject matter that Applicants regard as their invention. New independent claim 231 (and claims dependent therefrom) recites a method of preventing a RSV infection in human subject comprising administering to the subject a sustained release formulation comprising a fragment of palivizumab that immunospecifically binds to a RSV antigen. New independent claim 232 (and claims dependent therefrom) recites a method of treating or ameliorating one or more symptoms associated with a RSV infection in human subject comprising administering to the subject a sustained release formulation comprising a fragment of palivizumab that immunospecifically binds to a RSV antigen. New independent claim 235 (and claims dependent therefrom) recites a method of preventing a RSV infection in a human subject comprising administering to the subject a pharmaceutical composition adapted for pulmonary delivery comprising a fragment of palivizumab that immunospecifically binds to a RSV antigen. New independent claim 236 (and claims dependent therefrom) recites a method of treating or ameliorating one or more symptoms associated with a RSV infection in human subject comprising administering to the subject a pharmaceutical composition adapted for pulmonary delivery comprising a fragment of palivizumab that immunospecifically binds to a RSV antigen. New independent claims 257

and 258 recite a method of preventing a RSV infection, or treating or ameliorating one or more symptoms associated with a RSV infection in a human subject comprising administering to the lungs of the human subject a prophylactically or therapeutically effective amount of a composition comprising a fragment of palivizumab that immunospecifically binds to a RSV antigen. The amended claims and the new claims are fully supported by the specification of the present application, see, *e.g.*, page 20, lines 19-22, page 23, lines 3-6, page 24, lines 1-5, page 24, lines 23-29, page 25, lines 2-10, page 42, lines 22-32, and page 83, lines 21-34, and do not constitute new matter. Upon entry of this amendment, claims 73, 74, 85-94, 99-110, 180, 181, 186, 189-191 and 231-263 will be pending in the present application.

Applicants respectfully request that the amendments and remarks made herein be entered and fully considered.

1. THE CLAIM OBJECTIONS SHOULD BE WITHDRAWN

Claims 89, 91 and 187 are objected to because the word "intravenously" is misspelled. Applicants have amended claims 89 and 91 to correct the spelling of the word "intravenously" and Applicants have canceled claim 187, without prejudice. The cancellation of claim 187 and amendments to claims 89 and 91 have obviated the objection. Accordingly, the objection of claims 89, 91 and 187 is moot and should be withdrawn.

2. THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claim 187 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point and distinctly claim the subject mater which Applicants regard as the invention. Applicants have canceled claim 187, without prejudice. The cancellation of claim 187 has obviated the rejection under 35 U.S.C. § 112, second paragraph. Accordingly, the rejection of claim 187 under 35 U.S.C. § 112, second paragraph, is moot and should be withdrawn.

3. THE REJECTIONS UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

Claims 73, 85, 86, 89, 90, 91, 92, 99, 100 and 103-106 are rejected under 35 U.S.C. § 103(a) as being unpatentable over MedImmune, Inc. Synagis® package insert (hereinafter the "Package Insert") in view of Lam et al., 1997, *Proc. Int'l Symp. Rel. Bioact.*

Mater. 24:759-760 (hereinafter "Lam") for the reasons of record. As set forth in Paper No. 13, the Examiner contends that: (1) the Package Insert describes the administration of Synagis® (palivizumab) to pediatric patients less than two years old; and (2) Lam describes sustained release microencapsulation pharmaceutical formulations of a recombinant humanized anti-VEGF Fab fragment. The Examiner alleges that it would have been *prima facie* obvious to administer the antibodies described in the Package Insert in a sustained release vehicle as taught by Lam. For the reasons detailed below, the rejection of claims 73, 85, 86, 89, 90, 91, 92, 99, 100 and 103-106 under 35 U.S.C. § 103(a) cannot stand and should be withdrawn.

In order to expedite the prosecution of the application and without conceding to the validity of the rejection, Applicants have amended claim 73 (and claims dependent therefrom) to recite a sustained release formulation comprising palivizumab. Applicants have also added new claims 231-234, 239-242, 245, 246 and 249-252, directed to a method of preventing a RSV infection, or treating or ameliorating one or more symptoms associated with a RSV infection in a human subject comprising administering to the subject a sustained release formulation comprising a fragment of palivizumab that immunospecifically binds to a RSV antigen.

None of the references cited in the Office Action, alone or in combination, teach or suggest the presently claimed invention. The Package Insert sets forth a description of Synagis® (palivizumab) and the intramuscular administration of Synagis® to prevent a RSV infection in pediatric patients. The Package Insert does not teach or suggest sustained release formulations comprising palivizumab, much less methods of preventing a RSV infection, or treating or ameliorating a symptom associated with a RSV infection by administering such formulations to a human subject. Thus, the Package Insert does not render obvious presently pending claims 73, 85, 86, 89-92, 99, 100 and 103-106, directed to a sustained release formulation comprising palivizumab, or a method of preventing a RSV infection or treating or ameliorating one or more symptoms associated with a RSV infection comprising administering such a sustained release formulation. Moreover, the Package Insert does not teach or suggest methods of preventing a RSV infection, or treating or ameliorating a symptom associated with a RSV infection by administering to a human subject a sustained release formulation comprising a fragment of palivizumab that immunospecifically binds to a RSV antigen. Thus, the Package Insert does not render obvious presently pending claims 231-234, 239-242, 245, 246, 249-252, directed to a method of preventing a RSV infection, or

treating or ameliorating one or more symptoms associated with a RSV infection comprising administering to a human subject a sustained release formulation comprising a fragment of palivizumab that immunospecifically binds to a RSV antigen.

Lam does not cure the deficiencies in the Package Insert. Lam merely describes a controlled release formulation for an anti-VEGF Fab fragment. Lam does not describe or suggest a formulation for the sustained release of a humanized RSV monoclonal antibody such as palivizumab. As previously discussed in Paper No. 14, a ***humanized RSV monoclonal antibody*** such as palivizumab is ***structurally and functionally different*** from a ***Fab fragment*** of a ***VEGF*** monoclonal antibody. Lam only describes manipulation of various parameters with respect to a specific Fab fragment of a VEGF humanized monoclonal antibody. Indeed, many of the parameters that Lam manipulated to achieve microencapsulation of the Fab fragment of the VEGF humanized monoclonal antibody for controlled release were dependent on factors such as the stability and the size of the Fab fragment, and would not be expected by one of skill in the art to be applicable to the entire VEGF humanized monoclonal antibody, much less a humanized monoclonal antibody immunospecific for a RSV antigen such as palivizumab. Applicants submit that humanized monoclonal antibodies such as palivizumab (an IgG_{1K} monoclonal antibody) would have a different structure, function or pharmacokinetic profile than the VEGF Fab fragment described in Lam. Thus, one of skill in the art would not have been motivated to combine the teachings of Lam with the Package Insert to produce a sustained release formulation comprising palivizumab. Moreover, based upon Lam, one of skill in the art would not have had a reasonable expectation that the controlled release formulation described in Lam could be successfully applied to palivizumab. Accordingly, Lam, alone or in combination with the Package Insert, does not render obvious presently pending claims 73, 85, 86, 89-92, 99, 100 and 103-106, directed to a sustained release formulation comprising palivizumab, or a method of preventing a RSV infection, or treating or ameliorating one or more symptoms associated with a RSV infection comprising administering to a human subject such a sustained release formulation.

Moreover, Lam does not teach or suggest a method of preventing a RSV infection, or treating or ameliorating one or more symptoms associated with a RSV infection in a human subject comprising administering to the subject a sustained release formulation comprising a fragment of palivizumab that immunospecifically binds to a RSV antigen. As discussed above, Lam merely describes a controlled release formulation for an anti-VEGF Fab fragment. Applicants submit that a fragment of palivizumab that immunospecifically

binds to a RSV antigen would have a different function than the VEGF Fab fragment described by Lam, and the palivizumab fragment may have a different structure than the VEGF Fab fragment. The anti-VEGF Fab fragment described in Lam binds to vascular endothelial growth factor (VEGF), a cytokine ***normally*** found in human subjects that induces angiogenesis and endothelial cell proliferation. In contrast, the fragments of palivizumab encompassed by the presently pending claims immunospecifically bind to a RSV antigen, which is ***not normally*** found in human subjects. As a result of the normal expression pattern of cytokines in human subjects, factors, such as the systemic effect on the inhibition of blood vessel formation, need to be considered when administrating an antibody that immunospecifically binds to a cytokine that do not need to be considered when administering an anti-RSV monoclonal antibody such as palivizumab. Given the functional differences between a palivizumab fragment that immunospecifically binds to a RSV antigen and the anti-VEGF Fab fragment described by Lam, Applicants submit that one of skill in the art would reasonably expect that there would be differences in the composition of a sustained release formulation for a palivizumab fragment and the anti-VEGF Fab fragment described by Lam and that different doses would be needed to achieve the prophylactic or therapeutic effect desired (*i.e.*, the prevention or treatment of a RSV infection in the case of palivizumab fragments and the inhibition of angiogenesis in case of the anti-VEGF Fab fragment described by Lam). Thus, Applicants submit that one of skill in the art would not have been motivated to combine the teaching of the Package Insert regarding the intramuscular administration of Synagis® to prevent a RSV infection in pediatric patients with the teaching of Lam regarding controlled release to arrive at the presently claimed invention. Obviousness "cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination," and "teachings of references can be combined only if there is some suggestion or incentive to do so." *In re Fine* 837 F.2d 1071, 1075 (Fed. Cir. 1988). Accordingly, Lam, alone or in combination with the Package Insert, does not render obvious presently pending claims 231-234, 239-242, 245, 246 and 249-252, directed to a method of preventing a RSV infection, or treating or ameliorating one or more symptoms associated with a RSV infection in a human subject comprising administering to the subject a sustained release formulation comprising a fragment of palivizumab that immunospecifically binds to a RSV antigen.

Claims 74, 87, 88, 93, 94, 101, 102, 107-110, 180, 181, 186, 187, 189, 190 and 191 are rejected under 35 U.S.C. § 103(a) as being unpatentable over the Package Insert in view of Lam and further in view of Gonzalez et al., U.S. Patent No. 6,117,980 (hereinafter

"Gonzalez"). The Examiner contends that: (1) the Package Insert describes the administration of Synagis® (palivizumab) to pediatric patients less than two years old; (2) Lam describes sustained release microencapsulation pharmaceutical formulations of a recombinant humanized anti-VEGF Fab fragment; and (3) "Gonzalez teaches the administration of a humanized anti-IL-8 monoclonal antibody or fragments thereof via therapeutic formulation methods, such as inhalation, injection, intramusclar and sustained release." The Examiner alleges that one of skill in the art would have been "motivated to use a method of inhalation to administer palivizumab to the lungs because Gonzalez teaches known methods of preparing humanized antibodies or fragments thereof." The Examiner also alleges that one of skill in the art would have had "a reasonable expectation of success that palivizumab would work in a therapeutic formulation for inhalation because Gonzalez administers a humanized antibody and fragments thereof by inhalation." For the reasons detailed below, the rejection of claims 74, 87, 88, 93, 94, 101, 102, 107-110, 180, 181, 186, 187, 189, 190 and 191 under 35 U.S.C. § 103(a) cannot stand and should be withdrawn.

In order to expedite the prosecution of the application and without conceding to the validity of the rejection, Applicants have canceled claim 187, without prejudice, and amended claim 74 (and claims dependent therefrom) to recite a pharmaceutical composition adapted for pulmonary delivery comprising palivizumab. Applicants have also amended claims 180 and 181 (and claims dependent therefrom) to recite a method of preventing a RSV infection, or treating or ameliorating one or more symptoms associated with a RSV infection in a human subject comprising administering to the lungs of the human subject a prophylactically or therapeutically effective amount of a composition comprising palivizumab. Applicants have also added new claims 235-238, 243, 244, 247, 248 and 254-256, directed to a method of preventing a RSV infection, or treating or ameliorating one or more symptoms associated with a RSV infection in a human subject comprising administering a pharmaceutical composition adapted for pulmonary delivery comprising a fragment of palivizumab that immunospecifically binds to a RSV antigen. Further, Applicants have added new independent claims 257 and 258 (and claims dependent therefrom) to recite a method of preventing a RSV infection, or treating or ameliorating one or more symptoms associated with a RSV infection in a human subject comprising administering to the lungs of the human subject a prophylactically or therapeutically effective amount of a composition comprising a fragment of palivizumab that immunospecifically binds to a RSV antigen.

The Package Insert does not teach or suggest pharmaceutical compositions adapted for pulmonary delivery comprising palivizumab, much less methods of preventing a RSV infection, or treating or ameliorating a symptom associated with a RSV infection by administering such compositions to the lungs of a human subject. Thus, the Package Insert does not render obvious presently pending claims 74, 87, 88, 93, 94, 101, 102 and 107-110, directed to a pharmaceutical composition adapted for pulmonary delivery comprising palivizumab, or a method of preventing a RSV infection, or treating or ameliorating one or more symptoms associated with a RSV infection comprising administering to the lungs of a human subject such a pharmaceutical composition. Moreover, the Package Insert does not teach or suggest methods of preventing a RSV infection, or treating or ameliorating a symptom associated with a RSV infection by administering to the lungs of a human subject a pharmaceutical composition comprising a fragment of palivizumab that immunospecifically binds to a RSV antigen. Thus, the Package Insert does not render obvious presently pending claims 235-238, 243, 244, 247, 248 and 254-256, directed to a method of preventing a RSV infection, or treating or ameliorating one or more symptoms associated with a RSV infection comprising administering to the lungs of a human subject a pharmaceutical composition comprising a fragment of palivizumab that immunospecifically binds to a RSV antigen.

Further, the Package Insert does not teach or suggest a method of preventing a RSV infection, or treating or ameliorating a symptom associated with a RSV infection in a human subject by administering to the lungs of the subject a first dose of a prophylactically or therapeutically effective amount of a composition comprising palivizumab, said effective amount resulting in a concentration of at least 20 ng per mg of lung protein at least 20 days after administration of the first dose and before the administration of a subsequent dose. Thus, the Package Insert does not render obvious presently pending claims 180, 181, 186,189-191 and 257-263, directed to a method of preventing a RSV infection, or treating or ameliorating a symptom associated with a RSV infection in a human subject by administering to the lungs of the subject a first dose of a prophylactically or therapeutically effective amount of a composition comprising palivizumab or a palivizumab fragment that immunospecifically binds to a RSV antigen, said effective amount resulting in a concentration of at least 20 ng per mg of lung protein at least 20 days after administration of the first dose and before the administration of a subsequent dose.

Neither Lam nor Gonzalez cure the deficiencies in the Package Insert. As discussed above, Lam merely describes a controlled release formulation for an anti-VEGF Fab fragment. Gonzalez describes humanized anti-IL-8 monoclonal antibodies, compositions

comprising such antibodies and methods of treating inflammatory disorders utilizing such antibodies. Gonzalez merely provides generic teaching regarding therapeutic formulation methods and does not provide specific teaching regarding the delivery of anti-IL-8 antibodies to the lungs of subjects. Neither Lam nor Gonzalez teach or suggest pharmaceutical compositions adapted for pulmonary delivery comprising palivizumab, much less methods of preventing a RSV infection, or treating or ameliorating a symptom associated with a RSV infection by administering to the lungs of a human subject such compositions or pharmaceutical compositions comprising a fragment of palivizumab that immunospecifically binds to a RSV antigen. Moreover, neither Lam nor Gonzalez teach or suggest a method of preventing a RSV infection, or treating or ameliorating a symptom associated with a RSV infection in a human subject by administering to the lungs of the subject a first dose of a ~~prophylactically or therapeutically effective amount of a composition comprising~~ palivizumab or a palivizumab fragment that immunospecifically binds to a RSV antigen, said effective amount resulting in a concentration of at least 20 ng per mg of lung protein at least 20 days after administration of the first dose and before the administration of a subsequent dose.

Applicants submit that palivizumab or a palivizumab fragment that immunospecifically binds to a RSV antigen would have a different function than the anti-VEGF Fab fragment described by Lam or the humanized anti-IL-8 antibodies described by Gonzalez, and the palivizumab fragment may have a different structure than the anti-VEGF Fab fragment or the humanized anti-IL-8 antibodies. The anti-VEGF Fab fragment described by Lam and the humanized anti-IL-8 antibodies described by Gonzalez bind to cytokines ***normally*** found in human subjects. In contrast, palivizumab and the palivizumab fragments encompassed by the presently pending claims immunospecifically bind to a RSV antigen, which is ***not normally*** found in human subjects. When administering an antibody that immunospecifically binds to a cytokine, factors that need not be considered for an antibody that immunospecifically binds to a RSV antigen need to be considered. For example, the systemic effects on the regulation of blood vessel formation and the regulation of the subject's immune response need to be considered when administering an antibody that immunospecifically binds to a cytokine such as VEGF and IL-8, respectively.

Given the functional differences between palivizumab or a palivizumab fragment that immunospecifically binds to a RSV antigen and the anti-VEGF Fab fragment described by Lam and the humanized anti-IL-8 antibodies described by Gonzalez, Applicants submit that one of skill in the art would reasonably expect that there would be differences in

the structure of a composition comprising palivizumab or a palivizumab fragment and a composition comprising the anti-VEGF Fab fragment described by Lam or the humanized anti-IL-8 antibodies described by Gonzalez and that different methods of administration and different doses would be needed to achieve the prophylactic or therapeutic effect desired (*i.e.*, the prevention or treatment of a RSV infection in the case of palivizumab or a fragment thereof, the inhibition of angiogenesis in case of the anti-VEGF Fab fragment described by Lam, and the treatment of an inflammatory disorder in the case of the humanized anti-IL-8 antibodies described by Gonzalez). Thus, Applicants submit that one of skill in the art would not have been motivated to combine the teaching of the Package Insert regarding the intramuscular administration of Synagis® to prevent a RSV infection in pediatric patients with the teaching of Lam regarding controlled release and the teaching of Gonzalez regarding the administration of humanized anti-IL-8 antibodies to treat inflammatory disorders to arrive at the presently claimed invention. Accordingly, Gonzalez, alone or in combination with the Package Insert and/or Lam, does not render obvious presently pending claims 74, 87, 88, 93, 94, 101, 102, 107-110, 180, 181, 186,189-191, 235-238, 243, 244, 247, 248, 254-256 and 257-263.

In view of the foregoing, the rejections under 35 U.S.C. § 103(a) cannot stand and should be withdrawn.

4. MISCELLANEOUS

Applicants note that the rejection of claims 73 and 85-94 under 35 U.S.C. § 103(a) as being unpatentable over Johnson et al., 1997, *J. Infect. Dis.* 176:1215-1224 (hereinafter "Johnson") in view of Lam has been withdrawn. The Examiner states on page 2 of the Office Action that Applicants previous arguments were not persuasive but that the Johnson reference is withdrawn in attempt to simplify the rejection.

Applicants respectfully submit that the Johnson reference in combination with Lam does not render presently pending claims 73 and 85-94 obvious. Johnson describes the intramuscular or intravenous administration of palivizumab to cotton rats and the prophylactic effect achieved. There is no teaching in Johnson to produce a sustained release formulation or a pharmaceutical composition adapted for pulmonary delivery comprising palivizumab, much less a method of preventing a RSV infection, or treating or ameliorating a symptom associated with a RSV infection comprising administering to a human subject a sustained release formulation comprising palivizumab, or administering to the lungs of a human subject a pharmaceutical composition comprising palivizumab. The deficiencies in

Lam described above are not cured by Johnson. The combination of Johnson and Lam does not add anything more to the Examiner's rejection than the combination of the Package Insert and Lam. Thus, for the reasons presented above with respect to the combination of the Package Insert and Lam, the combination of Johnson and Lam does not render presently pending claims 73 and 85-94 obvious.

Applicants note that the rejection of claims 95-110, 180, 181, 186, 187 and 189-191 under 35 U.S.C. § 103(a) as being unpatentable over Johnson et al., 1997, *J. Infect. Dis.* 176:1215-1224 (hereinafter "Johnson") in view of the Package Insert and Lam has been withdrawn. The Examiner states on page 2 of the Office Action states that Applicants previous arguments were not persuasive but that the Johnson reference is withdrawn in attempt to simplify the rejection.

First, Applicants respectfully point out that claims 95-98 were canceled, without prejudice, in the Amendment filed on May 5, 2003, and claim 187 is canceled, without prejudice, in this Amendment. Applicants respectfully submit that the Johnson reference in combination with Lam does not render presently pending claims 99-110, 180, 181, 186, and 189-191 obvious. Johnson does not teach or suggest a method of preventing a RSV infection, or treating or ameliorating a symptom associated with a RSV infection in a human subject by administering to the lungs of the subject a first dose of a prophylactically or therapeutically effective amount of a composition comprising palivizumab, said effective amount resulting in a concentration of at least 20 ng per mg of lung protein at least 20 days after administration of the first dose and before the administration of a subsequent dose. There is no teaching or suggestion in Johnson to prevent or treat a RSV infection or ameliorate a symptom thereof in humans, much less a method of preventing or treating a RSV infection or ameliorate a symptom thereof, by administering to the lungs of a human subject a palivizumab composition. Moreover, there is no teaching or suggestion in Johnson regarding a method of preventing a RSV infection, or treating or ameliorating a symptom associated with a RSV infection by administering an amount of palivizumab effective to achieve a concentration of at least 20 ng per mg of lung protein at least 20 days after administration.

The deficiencies in Johnson are not cured by the secondary references. As discussed above, the Package Insert describes the intramuscular administration of Synagis® to prevent a RSV infection in pediatric patients and Lam describes a controlled release formulation for an anti-VEGF Fab fragment. Neither the Package Insert nor Lam teach or suggest a method of preventing a RSV infection, or treating or ameliorating a symptom

associated with a RSV infection in a human subject by administering to the lungs of the subject a first dose of a prophylactically or therapeutically effective amount of a composition comprising palivizumab, said effective amount resulting in a concentration of at least 20 ng per mg of lung protein at least 20 days after administration of the first dose and before the administration of a subsequent dose. The addition of the Johnson reference to the rejection of claims 99-110, 180, 181, 186, and 189-191 does not add anything more to the Examiner's allegations than the combination of the Package Insert and Lam or the combination of the Package Insert, Lam and Gonzalez. Thus, for the reasons presented above with respect to the combination of the Package Insert and Lam and the combination of the Package Insert, Lam and Gonzalez, the combination of Johnson, the Package Insert and Lam does not render presently pending claims 99-110, 180, 181, 186 and 189-191 obvious.

CONCLUSION

Applicants respectfully request entry and consideration of the foregoing remarks. Applicants believe that all of the present claims meet all of the requirements for patentability. Withdrawal of all rejections is requested.

If any issues remain, the Examiner is requested to telephone the undersigned at (858) 314-1200.

Respectfully submitted,

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